BIOGRAPHICAL SKETCH

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NAME: Jeffrey D. Lifson, MD

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Senior Principal Investigator and Director, AIDS and Cancer Virus Program, Leidos Biomedical Research, Inc., Frederick National Laboratory

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Northwestern University	B.S.Med.	June 1980	Pre-medicine, Philosophy, Art History
Northwestern University Medical School	M.D.	June 1982	Medicine
Stanford University Medical Center, Stanford, California		June 1983	Resident in Pathology
Department of Pathology, Stanford University Medical School and the Stanford Medical School Blood Center, Palo Alto, California.		July 1985	Postdoctoral Fellow

A. Personal Statement

My role in the program is to provide expertise and collaborative input on the design, execution, analysis, and interpretation of NHP studies and virologic assays. To this role, with background training in immunology and virology, I bring more than 30 years of experience in AIDS related research, including twenty years of experience in developing and applying AIDS-related NHP models. Expertise and contributions include pioneering the development and continuous refinement of methods for quantitative analysis of lentiviral infection, including in NHP models; and participation in numerous studies of the early stages of AIDS virus infection in such models, a pioneering role in the development of effective, sustainable cART regimens for use in NHP models, including regimens containing dolutegravir, tenofovir disproxil fumarate and emtricitabine, and the evaluation of "HIV cure" strategies. In addition, as Director of the AIDS and Cancer Virus Program of the Frederick National Laboratory, I oversee an integrated, interactive, multidisciplinary program with extensive expertise in all relevant areas of virologic analysis for NHP studies, from state of the art qPCR/qRT-PCR methods for viral nucleic acid quantification, to viral sequence analysis to tissue based analyses ranging from cutting edge in situ hybridization analyses (RNAScope/DNAScope), immunohistochemical and immunofluorescent confocal microscopy and laser capture microdissection capabilities (with Drs. Brandon Keele and Jake Estes in our program) and could potentially bring these resources to bear in support of the project, as needed.

B. Positions and Honors

Positions:

1985 – 1986: Associate Investigator, Department of Pathology and Laboratory Medicine, Palo Alto Veterans Administration Hospital/Stanford Medical School Blood Center, Palo Alto, CA
1986 – 1990: Senior Scientist, Director, Human Retrovirus Program, Genelabs Incorporated, Redwood City, CA
1990 – 1991: Acting Vice President, Research, Genelabs Incorporated, Redwood City, CA
1991 – 1995: Vice President, HIV and Exploratory Research, Genelabs Incorporated, Redwood City, CA
Senior Scientist, Head, Retroviral Pathogenesis Laboratory and Quantitative Molecular Diagnostics Section, AIDS Vaccine Program, SAIC Frederick, National Cancer Institute at Frederick, Frederick, MD

2001– 2002: Associate Director, AIDS Vaccine Program, and Senior Principal Scientist, Head, Retroviral Pathogenesis Laboratory and Quantitative Molecular Diagnostics Section, SAIC-Frederick, Inc., NCI-Frederick, Frederick, MD
2002 – 2008: Director, AIDS Vaccine Program, and Senior Principal Scientist, Head, Retroviral Pathogenesis Section, SAIC-Frederick, Inc., NCI Frederick, Frederick, MD
2008 – 2013: Senior Vice President, SAIC Frederick, Inc., Director, AIDS and Cancer Virus Program, and Senior Principal Scientist, Head, Retroviral Pathogenesis Section, SAIC-Frederick, Inc., Frederick National Laboratory for Cancer Research, Frederick, MD
2013 – Present: Senior Vice President, Leidos Biomedical Research, Inc., Director, AIDS and Cancer Virus Program, and Senior Principal Scientist, Head, Retroviral Pathogenesis Section, Leidos Biomedical Research, Inc., (Formerly SAIC-Frederick, Inc.) Frederick National Laboratory for Cancer Research, Frederick, MD

Honors

California Physicians National Merit Scholarship, 1976-1980
Summer Scholar, National Science Foundation, Committee for Advance Science Training, 1976
Paolo Raimondi Fellowship for the Study of Humanism in Medicine, Northwestern University Medical School, 1982
Postdoctoral Fellowship, The Damon Runyon-Walter Winchell Cancer Fund, 1983-1985
Associate Investigator Career Development Award, Veterans Administration, 1985-1986
SAIC Special Science Achievement Award, 1999
SAIC Outstanding Science Achievement Award, 2000
SAIC Technical Fellows Council Publication Prize, Biochemistry and Molecular Biology, 2007
Norman P. Salzman Mentoring Award, 2007
NIH Director's Award, 2012
Leidos Technical Fellows Council Publication Prize, Biochemistry and Molecular Biology, 2014
Leidos Biomedical Research, Inc., President's Award, 2014
Leidos Technical Fellows Council Publication Prize, Biochemistry and Molecular Biology, 2016

C. Contribution to Science

1. Defining the role of HIV Env/CD4 interactions in viral biology and pathogenesis, and potential treatment interventions:

I made important contributions to defining the key role of HIV Env/CD4 interactions in viral biology and pathogenesis at a time when this key aspect of biology of HIV was not well understood, demonstrating a key role for these interactions in viral binding and entry, and some forms of viral cytopathicity, along with showing the biological importance of the glycan component of the viral envelope glycoprotein in function. These findings and related work by others led to the development and evaluation of therapeutic approaches based on interfering with these processes, including a synthetic peptide based approach we pursued. Although CD4-based therapeutics have not developed into a clinically useful approach, understanding of HIV Env/CD4 interactions remains a fundamental foundation for efforts to develop both Env targeted vaccines and neutralizing monoclonal antibodies for prevention and treatment of HIV infection.

1: Lifson JD, Reyes GR, McGrath MS, Stein BS, Engleman EG. AIDS retrovirus induced cytopathology: giant cell formation and involvement of CD4 antigen. Science. 1986 May 30;232(4754):1123-7. PubMed PMID: 3010463.

2: Lifson JD, Feinberg MB, Reyes GR, Rabin L, Banapour B, Chakrabarti S, Moss B, Wong-Staal F, Steimer KS, Engleman EG. Induction of CD4-dependent cell fusion by the HTLV-III/LAV envelope glycoprotein. Nature. 1986 Oct 23-29;323(6090):725-8. PubMed PMID: 3095663.

3: Lifson J, Coutre S, Huang E, Engleman E. Role of envelope glycoprotein carbohydrate in human immunodeficiency virus (HIV) infectivity and virus-induced cell fusion. J Exp Med. 1986 Dec 1;164(6):2101-6. PubMed PMID: 3640800; PubMed Central PMCID: PMC2188479.

4: Lifson JD, Hwang KM, Nara PL, Fraser B, Padgett M, Dunlop NM, Eiden LE. Synthetic CD4 peptide derivatives that inhibit HIV infection and cytopathicity. Science. 1988 Aug 5;241(4866):712-6. PubMed PMID: 2969619.

2. Development and application of quantitative PCR for viral load measurements

I played a pioneering role in the development and application of quantitative PCR/RT PCR based measurements for assessing viral load in HIV infected individuals, developing one of the first approaches capable of rigorous quantitation of HIV nucleic acids by PCR based methods, applying this method to readily detect and quantify viral RNA in the plasma of all patients tested, including asymptomatic patients in whom HIV p24 antigen and viral culture assays were negative. Our determined viral RNA levels correlated with disease stage and CD4+ T cell counts, and showed readily demonstrable decreases in longitudinal specimens over the course of resolution of primary infection or short term AZT treatment. At a time when much of the field equated the asymptomatic clinically latent phase of HIV infection with virologic latency, based on negative results in HIV p24 antigen and viral culture assays, this work helped to fundamentally shift the conceptual

paradigm of HIV pathogenesis, recasting it as a continuous battle of attrition between viral replication and the immune system, with key ramifications for treatment decisions. This work also set the stage for the key role of nucleic acid based virologic assessment of new therapies as new drugs and combination therapies became available.

1: Piatak M Jr, Luk KC, Williams B, Lifson JD. Quantitative competitive polymerase chain reaction for accurate quantitation of HIV DNA and RNA species. Biotechniques. 1993 Jan;14(1):70-81. PubMed PMID: 8424881.

2: Piatak M Jr, Saag MS, Yang LC, Clark SJ, Kappes JC, Luk KC, Hahn BH, Shaw GM, Lifson JD. High levels of HIV-1 in plasma during all stages of infection determined by competitive PCR. Science. 1993 Mar 19;259(5102):1749-54. PubMed PMID: 8096089.

3: Piatak M Jr, Saag MS, Yang LC, Clark SJ, Kappes JC, Luk KC, Hahn BH, Shaw GM, Lifson JD. Determination of plasma viral load in HIV-1 infection by quantitative competitive polymerase chain reaction. AIDS. 1993 Nov;7 Suppl 2:S65-71. PubMed PMID: 7909227.

4: Wei X, Ghosh SK, Taylor ME, Johnson VA, Emini EA, Deutsch P, Lifson JD, Bonhoeffer S, Nowak MA, Hahn BH, et al. Viral dynamics in human immunodeficiency virus type 1 infection. Nature. 1995 Jan 12;373(6510):117-22. PubMed PMID: 7529365.

3. Development of vaccines capable of controlling and clearing SIV infection in macaques:

In a longstanding ongoing collaboration with Dr. L. Picker, I have helped to develop and characterize in NHP models novel vaccines based on the use of rhesus macaque CMV as a vaccine vector. I have led the in vivo virological characterization of the protective effects of these vaccines and participated in their immunological characterization. The vaccines induce unique, paradigm breaking immune responses and show an unprecedented ability to control, and ultimately clear highly pathogenic SIV infection in rhesus macaques. Further characterization of this vaccine approach in preclinical NHP models will be pursued in one of the current projects, while separate development efforts will lead to clinical evaluation.

1: Hansen SG, Vieville C, Whizin N, Coyne-Johnson L, Siess DC, Drummond DD, Legasse AW, Axthelm MK, Oswald K, Trubey CM, Piatak M Jr, Lifson JD, Nelson JA, Jarvis MA, Picker LJ. Effector memory T cell responses are associated with protection of rhesus monkeys from mucosal simian immunodeficiency virus challenge. Nat Med. 2009 Mar;15(3):293-9. doi: 10.1038/nm.1935. Epub 2009 Feb 15.

2: Hansen SG, Ford JC, Lewis MS, Ventura AB, Hughes CM, Coyne-Johnson L, Whizin N, Oswald K, Shoemaker R, Swanson T, Legasse AW, Chiuchiolo MJ, Parks CL, Axthelm MK, Nelson JA, Jarvis MA, Piatak M Jr, Lifson JD, Picker LJ. Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine. Nature. 2011 May 26;473(7348):523-7. doi: 10.1038/nature10003. Epub 2011 May 11. PubMed PMID: 21562493; PubMed Central PMCID: PMC3102768.

3: Hansen SG, Sacha JB, Hughes CM, Ford JC, Burwitz BJ, Scholz I, Gilbride RM, Lewis MS, Gilliam AN, Ventura AB, Malouli D, Xu G, Richards R, Whizin N, Reed JS, Hammond KB, Fischer M, Turner JM, Legasse AW, Axthelm MK, Edlefsen PT, Nelson JA, Lifson JD, Frueh K, Picker LJ. Cytomegalovirus vectors violate CD8+ T cell epitope recognition paradigms. Science. 2013 May 24;340(6135):1237874. doi: 10.1126/science.1237874. PubMed PMID: 23704576; PubMed Central PMCID: PMC3816976.

4: Hansen SG, Piatak M Jr, Ventura AB, Hughes CM, Gilbride RM, Ford JC, Oswald K, Shoemaker R, Li Y, Lewis MS, Gilliam AN, Xu G, Whizin N, Burwitz BJ, Planer SL, Turner JM, Legasse AW, Axthelm MK, Nelson JA, FrÃ¼h K, Sacha JB, Estes JD, Keele BF, Edlefsen PT, Lifson JD, Picker LJ. Immune clearance of highly pathogenic SIV infection. Nature. 2013 Oct 3;502(7469):100-4. doi: 10.1038/nature12519. Epub 2013 Sep 11.

4. Improved NHP models for HIV/AIDS studies:

I have played a key role in pioneering the development of novel NHP models for AIDS studies, including both a novel approach for generating clinically relevant chimeric SHIVs incorporating R5-tropic, transmitted/founder HIV-1 Env sequences, and minimally chimeric HIVs designed and adapted to overcome species specific host cell restrictions that normally limit replication of HIV in macaque cells. While experimental SIV infection of macaques is a very useful system for modeling many key aspects of HIV infection of humans, for some applications, such as evaluation of HIV Env targeted vaccines or antibodies, or antiviral agents active against HIV but not against SIV, it is not suitable. To address the need for NHP models for evaluation of HIV Env targeted interventions, investigators have developed chimeric viruses designated SHIVs (Simian/Human Immunodeficiency Viruses) that essentially consist of SIV in which the SIV Env sequence has been replaced by HIV Env sequence. While useful, many of the SHIVs developed to date were developed after extensive in vivo animal to animal passage, and do not accurately reflect the currently transmitted HIV Env sequences that sustain the pandemic and are the clinical targets of Env directed interventions. Most of these SHIVs are also not robustly pathogenic, further limiting their utility. With Drs. Paul Bieniasz and T. Hatziioannou we developed and applied an approach for generating SHIVs incorporating R5-tropic, transmitted/founder HIV-1 Env sequences, demonstrating mucosal transmissibility, in vivo replication and pathogenesis, and protection by passive monoclonal antibody immunoprophylaxis. This work added to the number of useful SHIVs for the field and established an approach that is being used to develop additional clinically relevant SHIVs, including with Clade C Env sequences. Also with Drs. Bieniasz and Hatziioannou, we have developed minimally chimeric HIVs, that contain limited SIV sequences designed and shown to help overcome some of the known species specific host cell restrictions that limit HIV replication in macaque cells and keep HIV infection of macaques from serving as a useful experimental model. Through in vitro recombinant engineering and in vivo adaptation we have generated viruses that are >95% HIV sequence, but are capable of high level, pathogenic replication in macaques,

leading to AIDS defining clinical endpoints. This model is being further developed for studies of vaccines, monoclonal antibody and antiretroviral drug interventions.

1: Del Prete GQ, Ailers B, Moldt B, Keele BF, Estes JD, Rodriguez A, Sampias M, Oswald K, Fast R, Trubey CM, Chertova E, Smedley J, LaBranche CC, Montefiori DC, Burton DR, Shaw GM, Markowitz M, Piatak M Jr, KewalRamani VN, Bieniasz PD, Lifson JD, Hatziioannou T. Selection of unadapted, pathogenic SHIVs encoding newly transmitted HIV-1 envelope proteins. Cell Host Microbe. 2014 Sep 10;16(3):412-8. doi: 10.1016/j.chom.2014.08.003. PubMed PMID: 25211081; PubMed Central PMCID: PMC4268878.

2: Hatziioannou T, Del Prete GQ, Keele BF, Estes JD, McNatt MW, Bitzegeio J, Raymond A, Rodriguez A, Schmidt F, Mac Trubey C, Smedley J, Piatak M Jr, KewalRamani VN, Lifson JD, Bieniasz PD. HIV-1-induced AIDS in monkeys. Science. 2014 Jun 20;344(6190):1401-5. doi: 10.1126/science.1250761. PubMed PMID: 24948736; PubMed Central PMCID: PMC4266393.

3: Hatziioannou T, Ambrose Z, Chung NP, Piatak M Jr, Yuan F, Trubey CM, Coalter V, Kiser R, Schneider D, Smedley J, Pung R, Gathuka M, Estes JD, Veazey RS, KewalRamani VN, Lifson JD, Bieniasz PD. A macaque model of HIV-1 infection. Proc Natl Acad Sci U S A. 2009 Mar 17;106(11):4425-9. doi: 10.1073/pnas.0812587106. Epub 2009 Mar 2. PubMed PMID: 19255423; PubMed Central PMCID: PMC2657417.

4: Hatziioannou T, Princiotta M, Piatak M Jr, Yuan F, Zhang F, Lifson JD, Bieniasz PD. Generation of simian-tropic HIV-1 by restriction factor evasion. Science. 2006 Oct 6;314(5796):95. PubMed PMID: 17023652.

5. Use of antiretroviral drug treatment in nonhuman primate models, characterization of residual virus under conditions of antiretroviral drug or host control, development of models for "HIV cure studies":

I have played a pioneering role in the development and application of antiretroviral drug treatment (ART) in NHP models, starting with pre/post-exposure prophylaxis studies, to studies in which short term post-infection ART was used to modulate the dynamics of the early virus/host balance to facilitate host control of infection, to the development of effective, sustainable cART regimens capable of achieving and maintaining clinically relevant levels of viral suppression (< 30 vRNA copies/mL plasma). Regimens we have developed with pharmaceutical collaborators have become the standard regimens employed by the field. We have also established and applied advanced methods for assessment of residual virus that persists in the face of seemingly effective suppressive cART and can give rise to recrudescent infection when cART is suspended. Together, these approaches constitute the development of the first useful NHP model for "HIV cure" studies, including interventions intended to target residual virus that persist despite cART. Given the unproven benefits and potential toxicities of some of the approaches proposed for "reservoir" targeted interventions, a reliable animal model is essential. We have developed a NHP model of cART suppressed SIV infection, with characterization of residual virus on cART, that is useful for such studies, demonstrating similarities of essential parameters between our NHP model and HIV infected humans on cART. We have also used this model to demonstrate the existence, in individuals spontaneously controlling infection ("elite controllers") and macaques on suppressive cART, of an immune privileged reservoir of infected T follicular helper cells in B cell follicles of secondary lymphoid tissues. Initial evaluations of reservoir targeting approaches in SIV infected macaques on suppressive cART, in the form of histone deacetylase inhibitors (Vorinostat/SAHA, Romidepsin), although disappointing in that while they showed demonstrable but only very modest in vivo activity, were nevertheless encouraging in the fact that this pattern of results recapitulated emerging clinical experience with these drugs.

1: Lifson JD, Rossio JL, Arnaout R, Li L, Parks TL, Schneider DK, Kiser RF, Coalter VJ, Walsh G, Imming RJ, Fisher B, Flynn BM, Bischofberger N, Piatak M Jr, Hirsch VM, Nowak MA, Wodarz D. Containment of simian immunodeficiency virus infection: cellular immune responses and protection from rechallenge following transient postinoculation antiretroviral treatment. J Virol. 2000 Mar;74(6):2584-93. PubMed PMID: 10684272; PubMed Central PMCID: PMC111746.

2: Del Prete G, Smedley J, Macallister R, Jones G, Li B, Hattersley J, Zheng J, Piatak M, Keele B, Hesselgesser J, Geleziunas R, Lifson J. Comparative evaluation of co-formulated injectable combination antiretroviral therapy regimens in SIV-infected rhesus macaques. AIDS Res Hum Retroviruses. 2015 Jul 6. [Epub ahead of print] PubMed PMID: 26150024.

3: Del Prete GQ, Oswald K, Lara A, Shoemaker R, Smedley J, Macallister R, Coalter V, Wiles A, Wiles R, Li Y, Fast R, Kiser R, Lu B, Zheng J, Alvord WG, Trubey CM, Piatak M Jr, Deleage C, Keele BF, Estes JD, Hesselgesser J, Geleziunas R, Lifson JD. Elevated plasma viral loads in romidepsin-treated Simian Immunodeficiency Virus-infected rhesus macaques on suppressive combination antiretroviral therapy. Antimicrob Agents Chemother. 2015 Dec 28;60(3):1560-72. doi: 10.1128/AAC.02625-15. PMID: 26711758

4: Fukazawa Y, Lum R, Okoye AA, Park H, Matsuda K, Bae JY, Hagen SI, Shoemaker R, Deleage C, Lucero C, Morcock D, Swanson T, Legasse AW, Axthelm MK, Hesselgesser J, Geleziunas R, Hirsch VM, Edlefsen PT, Piatak M Jr, Estes JD, Lifson JD, Picker LJ. B cell follicle sanctuary permits persistent productive simian immunodeficiency virus infection in elite controllers. Nat Med. 2015 Feb;21(2):132-9. doi: 10.1038/nm.3781. Epub 2015 Jan 19. PubMed PMID: 25599132; PubMed Central PMCID: PMC4320022.

D. Research Support

I am employed by Leidos Biomedical Research, Inc., the Prime Contractor for the Operations and Technical Support Contract to operate the Frederick National Laboratory on behalf of the National Cancer Institute and National Institutes of Health. My laboratory is supported with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E.